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APPLICATION NUMBER	FILING DATE	FIRST-NAMED APPLICANT	ATTY. DOCKET NO.
08/473847	6/7/95	NOE R	D-1-97CIP3

LAHIVE AND COCKFIELD
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18M1/0117

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1806	5

DATE MAILED: 01/17/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s) or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-21 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-21 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. The filing date of the instant claims is deemed to be the filing date of the instant application, i.e. 6/7/95, as the U.S. priority applications do not support the broader claims of the instant application (e.g. IgG1, functional attributes of gp39-specific antibodies, gp39-specific antibody/hybridoma species).

The PCT priority applications were not available to the examiner at this time and applicant has not provided copies for review.

3. The specification on page 1 should be amended to update the status of the various parent applications.

4. Formal drawings and photographs have been submitted which comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

For example, the disclosure is objected to because of the following informalities:
"BALB/c" is the proper designation of this mouse strain.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The specification is objected to and claims 9-17 and 20-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

It unclear if a cell line which produces an antibody having the exact structural and chemical identity of 3E4, 2H5, 2H8, 4D9-8, 4D9-9, 24-31, 24-43, 89-76 and 89-79 are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) a claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species. Deposit of the appropriate hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

8. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for while being enabling for the gp39 disclosed in the references cited on page 2, paragraph 3 of the instant specification, does not reasonably provide enablement for any "gp39. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not appear to specifically define the metes and bounds of "gp39". "gp39" is considered an ambiguous laboratory designation which does not clearly define a biological product. Furthermore, there are a number of members associated with the gp39 designation (i.e. glycoprotein having a 39 kDa molecular weight), each with its own distinctive structure and function. As such, these terms cannot be considered to be limited to the specific gp39 (i.e. CD40 ligand) disclosed in the specification. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable identification of any other gp39 protein meeting the functional limitations disclosed in the specification and intended by the claimed specificities and it is deemed to constitute undue experimentation to determine them. Applicant has enabled only for the gp39 (i.e. CD40 ligand) provided by the references cited on page 2, paragraph 3 of the instant specification. The disclosure is not commensurate in scope with the breadth of the claims.

In addition, applicant has not provided sufficient written description or enablement for any form of gp39 (i.e. CD40 ligand). Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, applicant has not provided sufficient sequence data and biochemical information to provided for all of the modifications that could be associated with gp39 or the CD40 ligand. Therefore, the problem of predicting protein structure from such limited information of a single protein and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed gp39 and, in turn, antibodies to said antigens in manner reasonably correlated with the scope of the claims broadly including any number of gp39 modifications. Again, the scope of the claims must bear a reasonable correlation with the scope of enablement. Without such guidance, the changes which can be made in the structure of an isolated gp39 and still maintain provide appropriate specificity for the activity of specific antibodies is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Alternatively, applicant may consider providing the appropriate sequence information to enable the gp39 encompassed by the instant claims. Applicant is reminded of the following.

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See *In re Fouche*, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

9. Claims 9-15 and 19-21 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "an epitope recognized" by certain gp39-specific antibodies because the characteristics of said recognized epitopes. In addition to linear sequences, epitopes may be conformation dependent and discontinuous, particularly with antibodies. However, applicant has not define or set forth the metes and bounds of said recognized epitopes. Further, antibodies that can inhibit the binding of the claimed antibody species may block said binding or other functional attributes via steric hindrance as well as via binding the same epitope. In addition, the claims recite "an epitope" which can imply that the antibodies recognize more than one epitope. These phrases also read on small amino acid sequences encompassed by linear or conformational epitopes which are incomplete regions of the epitopes bound by the claimed gp39-specific antibodies. There is insufficient guidance to any or all of the myriad antibodies that can bind an epitopes encompassed within this language; since the antibodies could bind either conformational or linear sequences as well as glycosylated epitopes; the antibodies are apparently determined by blocking assays which could indicate both steric hindrance and direct binding of the same epitope; and the antibodies could block only portions or irrelevant cross-reactive epitopes. One of the skill in the art would neither expect nor predict the appropriate functioning of the antibodies as broadly claimed. Applicant has only provided guidance as to the particular gp39-specific antibody species and not to the exact nature of the epitope bound by the claimed antibody species. It would require undue experimentation to determine said epitopes without clearly defining the metes and bounds of said epitopes.

The amendments must be supported by the specification so as not to add any new matter.

10. Claims 1-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-21 are indefinite in that they only describe the compositions of interest by an arbitrary protein name, that is, "gp39". gp39 is considered an ambiguous laboratory designation which does not clearly define a biological product. Furthermore, there are a number of members associated with the gp39 designation as it reads on any glycoprotein having a molecular weight of 39 kDa, each glycoprotein with its own distinctive structure and function. While the name themselves may have some notion of the biological property of the intended protein, there is nothing in the claims which distinctly claims the protein. Others in the field may isolate the same protein and give such an entirely different name (i.e. CD40 ligand). Applicant should particularly point out and distinctly claim the gp39 by claiming characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of.

B) Claims ??? are indefinite in the recitation of "3E4, 2H5, 2H8, 4D9-8, 4D9-9, 24-31, 24-43, 89-76 and 89-79" because their characteristics are not known. The use of recited laboratory designations for the claimed monoclonal antibodies and hybridomas as the sole means of identifying said antibodies and hybridomas renders the claims indefinite because these laboratory designations do not clearly define the claimed products. Different laboratories may use the same laboratory designations to define completely distinct cell lines, antibodies and hybridomas.

The amendments must be supported by the specification so as not to add any new matter.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1-21 are rejected under 35 U.S.C. § 103 as being unpatentable over Lederman et al. (U.S. Patent No. 5,474,771; 1449, #AA) or Lederman et al. (WO93/08207; 1449, #AB) or Armitage et al. (WO93/09812, 1449, #AC), or Aruffo et al. (EP 0555880; 1449, #AE) or Aruffo et al. (EP0585943; 1449, #AE), each alone or in combination and in further view of well known procedures and uses of antibodies and B cell proliferation assays as disclosed in the instant specification.

Lederman et al. ('771), Lederman et al. ('207), Armitage et al. ('812) and Aruffo et al. ('880) all teach the CD40 ligand (i.e. 5C8 antigen or gp39), its role in helper T cell activity and the use of antibodies to said CD40 ligand for characterizing its biological role, including inhibiting helper function as well as diagnostic and therapeutic tools. These references differ from the instant claims by not explicitly reciting antibodies of the IgG1 subclass or the particular antibodies of the instant inventions.

These references as well as the ordinary artisan either taught or employed standard assays to determine the function of inhibitory antibodies for T cell helper function, encompassing the functional limitations of the instant claims. Also, the use of various isotypes of antibodies including IgG1 was well known in the art the time the invention was made as different isotypes could either be substituted for one another or be preferred for the functional attributes of the constant regions. Therefore the generation and use of IgG1 antibodies was obvious at the time the invention was made. The primary references also exemplify inhibitory CD40 ligand-specific antibodies and contemplate CD40 ligand-specific antibodies generally. The claimed particular antibody/hybridoma species appear to be functionally equivalent of those antibodies exemplified and taught in the prior art

One of ordinary skill in the art at the time the invention was made would have been motivated to select gp39-specific IgG1 antibodies and evaluate their efficacy in various diagnostic and therapeutic regimen in treating human disease. Also such gp39-specific antibodies would have used to determine the functional attributes of the CD40 ligand in helper T function. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Therefore, the antibody compounds and compositions as well as the functional limitations of said gp39-specific antibodies encompassed by the claimed invention were obvious to one of ordinary skill in the art at the time the invention was made.

13. No claim is allowed.

14. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
January 15, 1997